**RE: GENERAL EFFICACY AND CLINICAL SAFETY INFORMATION FOR AMERGE® TABLETS**

## SUMMARY


- In three pivotal placebo-controlled clinical trials, Amerge® (naratriptan hydrochloride) Tablets 1 mg and 2.5 mg were significantly more effective than placebo in reducing moderate or severe headache pain to mild or no headache pain at four hours (1, 2, 3, 4).
- The overall incidence of adverse events in placebo-controlled studies after administration of *Amerge* Tablets 1 mg and 2.5 mg was generally low and comparable to placebo (5).


**Some information contained in this response may be outside the approved prescribing information for *Amerge*. This response is not intended to offer recommendations for administering *Amerge* in a manner inconsistent with its approved labeling. In order for GlaxoSmithKline to monitor the safety of *Amerge*, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the Prescribing Information for *Amerge*.**

## BACKGROUND

The clinical program for *Amerge* includes nine clinical studies in patients with migraine during which 4,557 patients treated over 15,000 attacks with various doses of *Amerge* (0.1 mg, 0.25 mg, 1 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg) (2, 3, 4, 6, 7, 8, 9, 10, 11). The efficacy of *Amerge* Tablets in the acute treatment of migraine headaches was evaluated in six randomized, double-blind, placebo-controlled studies of which four used the recommended dosing regimen and were conducted as outpatient trials. Three of these were pivotal trials and are included in the prescribing information for *Amerge* to support its efficacy in the treatment of migraine (2, 3, 4). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain (grade 2 or 3) to mild or no pain (grade 1 or 0), was assessed up to four hours after dosing.

Because *Amerge* Tablets may be distinguished from other currently marketed triptans by its duration of action and low recurrence rates, clinical data for *Amerge* has focused on the prospectively defined primary endpoint of 4 hours and beyond (8, 12, and 24 hours).

## DOSE RANGING TRIAL

### Multinational, Single-Attack Trial

Havanka et al reported the results of a double-blind, placebo controlled dose ranging study with *Amerge* Tablets (6). A total of 643 IHS diagnosed migraineurs were randomized to treat a single attack with either 1 mg, 2.5 mg, 5 mg, 7.5 mg, or 10 mg *Amerge*, Imitrex® (sumatriptan succinate) 100 mg, or placebo.

Headache response at four hours was observed in 64% (1mg), 63% (2.5 mg), 65% (5 mg), 80% (7.5 mg) and 80% (10 mg) of patients treated with *Amerge* compared with 80% for *Imitrex* 100 mg and 39% for patients treated with placebo ($P<0.05$ vs. placebo). Four-hour efficacy rates for clinical disability, and the elimination of associated symptoms (nausea, photophobia, and phonophobia) were similar to those for headache response at each study drug dose. Significantly fewer patients taking *Amerge* 2.5 mg (17%) experienced headache recurrence compared with *Imitrex* 100 mg (44%).

## PIVOTAL CLINICAL TRIALS

### Study 1 (U.S Single-Attack Trial)

Klassen et al reported the results of a phase III, randomized, double-blind, single-attack, outpatient study conducted in adult migraineurs (3). It included two lower doses of *Amerge* Tablets (0.1 mg and 0.25 mg) as well as 1 mg and 2.5 mg doses in an attempt to identify the minimum effect and no effect doses. Results are summarized in Table 1.

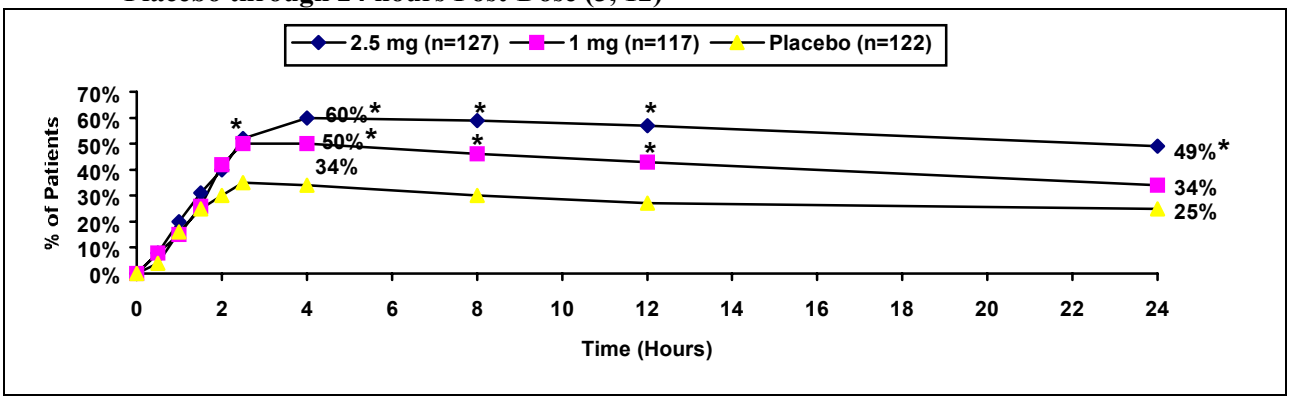
**Table 1. Efficacy of *Amerge* Tablets in the Treatment of Migraine (3, 12)**

| | | ***Amerge* Tablets** | | | |
|---|---|---|---|---|---|
| **Parameter** | **Placebo (n=122)** | **0.1 mg (n=128)** | **0.25 mg (n=119)** | **1 mg (n=117)** | **2.5 mg (n=127)** |
| | **4 hour Parameters** | | | | |
| Headache Response | 34% | 32% | 35% | 50%*† | 60%*†‡ |
| Headache Resolution | 20% | 16% | 16% | 27%† | 33%*†‡ |
| Absence of Nausea | 59% | 49% | 51% | 68%† | 71%*†‡ |
| Absence of Photophobia | 38% | 30% | 35% | 52%*† | 57%*†‡ |
| Absence of Phonophobia | 37% | 36% | 38% | 48%† | 57%*†‡ |
| Mild or Normal Clinical Disability | 48% | 48% | 47% | 63%*† | 70%*†‡ |
| | **24-hour Parameters[§]** | | | | |
| Headache Response at 24 hours | 25% | 28% | 29% | 34% | 49%*‡ |
| Absence of Nausea | 64% | 57% | 61% | 71% | 80% |
| Absence of Photophobia | 50% | 41% | 48% | 53% | 73% |
| Absence of Phonophobia | 43% | 40% | 44% | 44% | 57% |
| Rescue Medication | 56% | 53% | 52% | 38% | 31%*†‡ |
| Headache Recurrence | 38% | 39% | 38% | 39% | 28% |

*$P < 0.05$ vs. placebo
† $P < 0.05$ vs. 0.1 mg
‡ $P < 0.05$ vs. 0.25 mg.
§ Statistical analysis was not performed for headache recurrence or associated symptom data at 24 hours.

*Amerge* Tablets 2.5 mg and 1 mg were effective in relieving headache at four hours post-dose. Similar patterns of response were observed for associated symptoms and clinical disability. For patients that responded at four hours, response was maintained out to 24 hours as depicted in Figure 1.

**Figure 1. Percentage of Patients Reporting Headache Response after Treatment with *Amerge* or Placebo through 24 hours Post-Dose (3, 12)**




*P* < 0.05 vs. placebo; A last observation carried forward method was used.

**Study 2 (Multinational, Multiple-Attack Trial)**

The efficacy and tolerability of *Amerge* and *Imitrex* were compared in a double-blind, placebo-controlled, multiple-attack, parallel group study. Patients were randomized to *Amerge* Tablets (0.1 mg, 0.25 mg, 1 mg and 2.5 mg), placebo or *Imitrex* 100 mg to treat up to three attacks (4).

A total of 1,222 patients treated at least one attack, 1,062 treated two attacks, and 930 treated three attacks. The total number of attacks treated was 3,222. Headache response at four hours post-dose was greater with *Imitrex* 100 mg and *Amerge* 1 mg and 2.5 mg compared with placebo. Statistically significant differences in headache response were observed between *Imitrex* and all doses of oral *Amerge*. *Amerge* 0.1 mg and 0.25 mg were ineffective. Relatively fewer patients receiving *Amerge* 2.5 mg (19%) experienced headache recurrence compared with *Imitrex* 100 mg (36%) for attack 1. Data for attacks 2 and 3 are similar to that for Attack 1. Results are summarized in Table 2.

**Table 2. Efficacy in Migraineurs Using *Amerge* Tablets (0.1 to 2.5 mg), *Imitrex* Tablets 100 mg, or Placebo to Treat up to Three Migraine Attacks; Attack 1 (4, 13)**

| | Placebo | *Imitrex* Tablets | *Amerge* Tablets | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **(n= 104)** | **100 mg (n=229)** | **0.1 mg (n=207)** | **0.25 mg (n=214)** | **1 mg (n=208)** | **2.5 mg (n=199)** |
| | **4-hour parameters** | | | | | |
| Headache Response | 27% | 76%† | 36% | 36% | 52%* | 66%*‡ |
| Headache Resolution | 10% | 56%† | 17% | 16% | 26%* | 43%*‡ |
| Absence of Nausea | 56% | 79% | 63% | 61% | 71%* | 77%* |
| Absence of Phonophobia/ photophobia | 34% | 77% | 42% | 39% | 57%* | 67%* |
| Mild or Normal Clinical Disability | 49% | 78% | 50% | 52% | 62%* | 72%* |
| | **24-hour parameters§** | | | | | |
| Headache Response at 24 hours‖ | 35% | ND | ND | ND | 55% | 67% |
| Absence of Nausea | 78% | 93% | 84% | 84% | 92% | 92% |
| Absence of Phonophobia/ photophobia | 68% | 90% | 75% | 79% | 82% | 90% |
| Rescue Medications | 70% | 44%¶ | 68% | 66% | 57%* | 42%*‡ |
| Headache Recurrence | 10% | 36% | 39% | 43% | 42% | 19% |

* $P < 0.05$ vs. placebo † $P < 0.05$ vs. 0.1 mg, 0.25 mg, 1 mg. 2.5 mg *Amerge* Tablets ‡ $P < 0.05$ vs. 1 mg *Amerge* Tablets
§ Statistical analysis was not performed for headache recurrence, headache response or associated symptom data at 24 hours.
‖ Patients were considered treatment failures if they took a second dose or rescue medication only up to 4 hours post-dose
¶ $P < 0.05$ vs. 0.1 mg, 0.25 mg, 1 mg *Amerge* Tablets

*Amerge* Tablets 2.5 mg and 1 mg were effective in relieving headache at four hours post-dose. Similar patterns of response were observed for associated symptoms and clinical disability. For patients that responded at four hours, response was maintained out to 24 hours. Relatively fewer patients receiving *Amerge* Tablets 2.5 mg experienced headache recurrence. Seventy nine percent and 88% of patients treated with *Amerge* Tablets 1 mg and 2.5 mg, respectively, responded in at least one of three distinct migraine attacks compared with 55% of patients treated with placebo. Seventy-two percent and 50% of patients treated with *Amerge* Tablets 2.5 and 1 mg, respectively, responded in at least two of three distinct migraine attacks compared with 22% of patients treated with placebo.

**Study 3 (U.S. Multiple-Attack Trial)**

A double-blind, placebo-controlled, four-period *crossover* group trial evaluated the efficacy and tolerability of 0.25 mg, 1 mg or 2.5 mg of *Amerge* Tablets or placebo in the treatment of up to four attacks (2). A second, identical dose could be taken to treat recurrence (subjective worsening of headache following initial response). A total of 682, 632, 561, and 514 patients treated one, two, three, or four attacks, respectively. Across all attacks the percentage of patients achieving headache response at four hours post-dose, was 57% and 68% for *Amerge* Tablets 1 mg and 2.5 mg, respectively, compared with 33% of patients treated with placebo. A significantly greater percentage of patients taking both *Amerge* Tablets 1 mg and 2.5 mg reported headache response compared with placebo. The 2.5 mg dose was superior to the 1 mg dose. The efficacy and tolerability of *Amerge* Tablets in Study 3 is summarized below in Table 3.

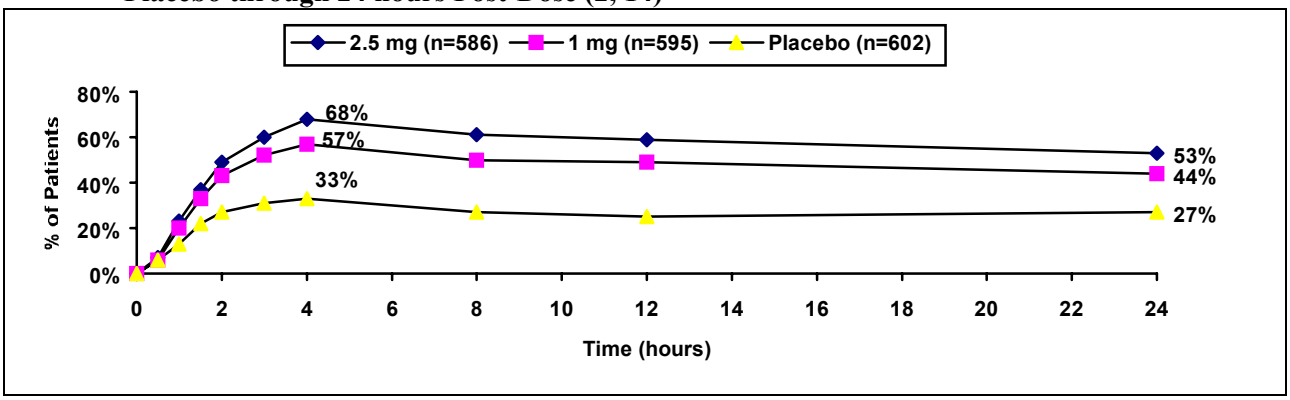
**Table 3. Efficacy Across All Attacks in Migraineurs Using *Amerge* Tablets or Placebo to Treat up to Four Migraine Attacks (2, 14)**

| | **Placebo** | ***Amerge* Tablets** | | |
|---|---|---|---|---|
| **Parameter** | **(n=602)** | **0.25 mg (n=591)** | **1 mg (n=595)** | **2.5 mg(n=586)** |
| | **4 Hour Parameters** | | | |
| Headache Response | 33% | 39% | 57%*† | 68%*† |
| Headache Resolution | 15% | 20% | 33%*† | 45%*† |
| Absence of Nausea | 54% | 58% | 69%*† | 75%*† |
| Absence of Photophobia | 33% | 39% | 53%*† | 61%*† |
| Absence of Phonophobia | 36% | 43% | 55%*† | 65%*† |
| Mild or Normal Clinical Disability | 50% | 56% | 70%*† | 76%*† |
| | **24-Hour Parameters‡** | | | |
| Headache Response at 24 hours | 27% | 32% | 44%*† | 53%*† |
| Absence of Nausea | 62% | 68% | 77% | 82% |
| Absence of Photophobia | 46% | 51% | 64% | 72% |
| Absence of Phonophobia | 49% | 54% | 66% | 74% |
| Rescue Medication | 52% | 48% | 34%*† | 26%*† |
| Headache Recurrence | 36% | 34% | 33% | 27% |

* $P < 0.05$ vs. placebo
† $P < 0.05$ vs. 0.25 mg
‡ Statistical analysis was not performed for headache recurrence or associated symptom data at 24 hours.

*Amerge* Tablets 2.5 mg and 1 mg were effective in relieving headache at four hours post-dose. Similar patterns of response were observed for associated symptoms and clinical disability. For patients that responded at four hours, response was maintained out to 24 hours, as depicted in Figure 2.

**Figure 2. Percentage of Patients Reporting Headache Response after Treatment with *Amerge* or Placebo through 24 hours Post-Dose (2, 14)**




*P* < 0.05 vs. placebo for both doses from 60 minutes through 24 hours. A last observation carried forward method was used.

## ADVERSE EVENTS IN CLINICAL TRIALS

Table 4 lists adverse events that occurred in five placebo-controlled clinical trials of approximately 1752 exposures to placebo and *Amerge* Tablets in adult migraine patients as depicted in the product labeling for *Amerge*. Only events that occurred at a frequency of 2% or more in the *Amerge* Tablets 2.5 mg treatment group and were more frequent in that group than in the placebo group are included.

**Table 4. Treatment-Emergent Adverse Events Reported by at Least 2% of Patients in Placebo-Controlled Migraine Trials (1)**

| Adverse Event Type | Placebo (n = 498) | *Amerge* 1 mg (n = 627) | *Amerge* 2.5 mg (n = 627) |
|---|---|---|---|
| Atypical sensation | 1% | 2% | 4% |
| Paresthesias (all types) | <1% | 1% | 2% |
| Gastrointestinal | 5% | 6% | 7% |
| Nausea | 4% | 4% | 5% |
| Neurological | 3% | 4% | 7% |
| Dizziness | 1% | 1% | 2% |
| Drowsiness | <1% | 1% | 2% |
| Malaise/fatigue | 1% | 2% | 2% |
| Pain and pressure sensation | 2% | 2% | 4% |
| Throat/neck symptoms | 1% | 1% | 2% |

A summary of the most frequent adverse events in seven placebo/active-controlled trials and one open-label trial are depicted in Table 5. The overall incidence of cardiovascular, chest-related symptoms, and neurologic adverse events for *Amerge* Tablets in controlled clinical trials was comparable to the placebo rate (1, 15). The incidence of serious adverse events and the percentage of patients who withdrew because of serious adverse events were <1%.

**Table 5. Summary of Most Frequent Adverse Events* in 7 Placebo-Controlled Trials and 1 Open-Label Trial with *Amerge* Tablets (15)**

| | Controlled Studies† | | | Open-Label‡ |
|---|---|---|---|---|
| **Symptom** | **Placebo (N=846)** | ***Amerge* 1 mg (N=910)** | ***Amerge* 2.5 mg (N=919§)** | ***Amerge* 2.5 mg (N=417)** |
| Nausea | 6% | 5% | 5% | 3% |
| Vomiting | 9% | 6% | 5% | <1% |
| Malaise/Fatigue | <1% | 1% | 3% | 1% |
| Dizziness | 2% | 1% | 2% | <1% |
| Migraine | 2% | 2% | 2% | <1% |
| Drowsiness/Sleepiness | <1% | <1% | 2% | 2% |
| Tingling | <1% | <1% | 1% | <1% |
| Hyposalivation | <1% | <1% | 1% | 2% |

*Events with >1% occurrence are reported
†Percentage of patients with adverse events
‡Percentage of attacks with adverse events
§Patients taking one dose

*Amerge* Tablets are generally well tolerated. Most adverse reactions are mild and transient.

**REV0805**

## REFERENCES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**Enclosure: Prescribing Information for *Amerge* Tablets**